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Contribution of VEGF and miR-21 in mediating the regenerative effects of mesenchymal stromal cell secretome on spermatogenesis restoration

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Multipotent mesenchymal stromal cells (MSCs) represent a promising therapeutic approach for male infertility, with their regenerative properties largely attributed to paracrine signaling. Our previous work demonstrated that subtunical injection of MSC secretome restores spermatogenesis in murine models of testicular injury, and that neutralization of either vascular endothelial growth factor (VEGF) or microRNA-21 (miR-21) within the secretome attenuates this therapeutic effect. However, whether these factors individually suffice to replicate the full regenerative capacity of MSC secretome remains unresolved.

In the present study, we used a doxorubicin-induced murine model of testicular injury to assess spermatogenic recovery under four experimental conditions: (1) administration of human recombinant VEGF, (2) administration of a miR-21 mimic, (3) administration of complete human adipose-derived MSC secretome, and (4) no therapeutic intervention (damage control). Therapeutic outcomes were evaluated through histological analysis of seminiferous tubule morphology—categorized as normal, damaged, or recovering—and by quantification of total and motile epididymal spermatozoa.

Testicular injury resulted in a marked reduction in total sperm count and a complete loss of sperm motility relative to healthy controls. Treatment with the complete MSC secretome significantly improved both total and motile sperm counts and increased the proportion of normal seminiferous tubules. In contrast, neither VEGF nor miR-21 administered individually restored spermatogenic parameters to levels achieved with the complete MSC secretome. While miR-21 alone modestly increased total sperm number, it failed to recover sperm motility. VEGF alone did not enhance total sperm count but led to the appearance of isolated motile spermatozoa. Notably, neither factor alone influenced seminiferous tubule morphology or altered the distribution of normal, damaged, or recovering tubules.

These findings demonstrate that although VEGF and miR-21 are essential contributors to the regenerative effects of MSC secretome, they are insufficient as standalone therapeutics. Their full potential appears contingent upon synergistic interactions within the complex milieu of the complete secretome. This study underscores the limitations of single-factor strategies and supports the continued development of MSC secretome-based therapies for male infertility.

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